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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

ADDRESS TO: **Mail Stop RCE**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application No.	09/939,275
Filing Date	August 24, 2001
First Named Inventor	Adams
Group Art Unit	1634
Examiner Name	Chakrabarti, A.
Attorney Docket No.	EXT-062C1

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

NOTES

RCE v. CPA: 37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53(d) instead of a RCE to be eligible for the patent term adjustment provisions of the AIPA.

FEE AND SUBMISSION REQUIRED: A submission as used in this section includes, but is not limited to, an information disclosure statement, an amendment to the written description, claims, or drawings, new arguments, or new evidence in support of patentability. If reply to an Office action under 35 U.S.C. 132 is outstanding, the submission must meet the reply requirements of § 1.111 (see 37 C.F.R. 1.114 (c)).

RCE APPLIES TO: An application in which prosecution is closed (see 37 C.F.R. § 1.114 (b)).

RCE DOES NOT APPLY TO: (1) A provisional application; (2) an application for a utility or plant patent filed under 35 U.S.C. 111(a) before June 8, 1995; (3) an international application filed under 35 U.S.C. 363 before June 8, 1995; (4) an application for a design patent; or (5) a patent under reexamination (see 37 C.F.R. 1.114(e)).

1. SUBMISSION REQUIRED UNDER 37 C.F.R. § 1.114

a. ☐ Enter and consider the unentered amendment under 37 C.F.R. § 1.116 previously filed on _____.
b. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____.
c. ☒ Amendment/Response enclosed.
d. ☐ Affidavit(s)/Declaration(s) enclosed.
e. ☐ Information Disclosure Statement (IDS) enclosed.
   i. ☐ PTO-1449
   ii. ☐ Copies of IDS Citations
f. ☐ Other _____

2. RCE FEE REQUIRED UNDER 37 C.F.R. § 1.114

a. ☐ Small entity status
   i. ☐ was established in the prior nonprovisional application.
   ii. ☐ is established herewith by the enclosed written assertion of entitlement to small entity status.
b. ☐ A Petition and Fee for Extension of Time for _____ months up to and including _____ is enclosed herewith.
c. ☒ A check in the amount of $ 770.00 is enclosed.
d. ☐ The Commissioner is hereby authorized to charge the required fee(s), i.e., $____, to Deposit Account No. 20-0531.
e. ☒ The Commissioner is hereby authorized to credit overpayments or charge any additional fees required for this submission under 37 C.F.R. §§ 1.16 and 1.17 to Deposit Account No. 20-0531.

12/17/2003 AWONDAF1 00000041 09939275

01 FC:1801 770.00 OP

3. MISCELLANEOUS

a. ☒ Return Receipt Postcard enclosed.
b. ☒ Other Copy of Power of Attorney by Assignee of Entire Interest Revocation of Prior Powers and New Power of Attorney and related papers filed on November 20, 2003; Notice of Loss of Entitlement of Small Entity Status; Fee Transmittal; Transmittal Form.

CORRESPONDENCE ADDRESS	SIGNATURE BLOCK
Direct all correspondence to: Patent Administrator Testa, Hurwitz & Thibeault, LLP High Street Tower 125 High Street Boston, MA 02110 Tel. No.: (617) 248-7000 Fax No.: (617) 248-7100	Respectfully submitted, Date: December 15, 2003 Reg. No. 51,752 Tel. No.: (617) 310-8423 Fax No.: (617) 248-7100 Jennifer Grant Moitoso Attorney for Applicant(s) Testa, Hurwitz & Thibeault, LLP High Street Tower 125 High Street Boston, MA 02110

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FEE TRANSMITTAL
FY 2004

Complete if Known	
Application Serial Number	09/939,275
Filing Date	August 24, 2001
First Named Inventor	Adams
Group Art Unit	1634
Examiner Name	Chakrabarti, A.
Attorney Docket No.	EXT-062C1

METHOD OF PAYMENT

1. ☒ Payment Enclosed:
   ☒ Check ☐ Money Order ☐ Other

2. ☒ The Commissioner is hereby authorized to credit or charge any fee indicated below for this submission to Deposit Account No. 20-0531.
   ☐ Required Fees (copy of this sheet enclosed).
   ☒ Additional fee required under 37 CFR 1.16 and 1.17.
   ☒ Overpayment Credit.

3. ☐ Applicant claims small entity status.

FEE CALCULATION

1. FILING FEE

Large Entity Fee ($)	Fee Description	Fee Paid
770	Utility filing fee	
340	Design filing fee	
160	Provisional filing fee	

	Number Filed	Number Extra	Rate	Amount
Total Claims		- 20 =	x $ 18.00 =	
Independent Claims		- 3 =	x $ 86.00 =	
☐ Multiple Dependent Claim(s), if any			$290.00 =	

TOTAL:
SMALL ENTITY DISCOUNT:
SUBTOTAL (1) ($) 0.00

2. AMENDMENT CLAIM FEES

	Claims Remaining After Amend.	Highest No. Previously Paid For	Present Extra	Rate	Fee Paid
Total		-	=	x $ 18.00 =	
Indep.		-	=	x $ 86.00 =	
☐ First Presentation of Multiple Dep. Claim				+ $290.00 =	

TOTAL: ($)
SMALL ENTITY DISCOUNT: ($)
SUBTOTAL (2) ($)0.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee ($)	Small Entity Fee ($)	Fee Description	Fee Paid
130	65	Surcharge - late filing fee or oath	
50	25	Surcharge - late provisional filing fee or cover sheet	
130	130	Non-English specification	
2,520	2,520	Request for ex parte reexamination	
110	55	Extension for reply within first month	
420	210	Extension for reply within second month	
950	475	Extension for reply within third month	
1480	740	Extension for reply within fourth month	
2010	1005	Extension for reply within fifth month	
330	165	Notice of Appeal	
330	165	Filing a brief in support of an appeal	
290	145	Request for oral hearing	
130	130	Petitions to the Commissioner	
180	180	Submission of Information Disclosure Statement	
770	385	Filing a submission after final rejection (37 CFR 1.129(a))	
770	385	For each additional invention to be examined (37 CFR 1.129(b))	
100	100	Certificate of Correction for applicant's error	
110	55	Submission of Terminal Disclaimer	
Other fee (Specify)		Request for Continued Examination (RCE)	770.00
Other fee (Specify)			

SUBTOTAL (3) ($) 770.00

SUBTOTAL (1) 0
SUBTOTAL (2) 0
SUBTOTAL (3) 770.00

TOTAL ($) 770.00

CORRESPONDENCE ADDRESS

Direct all correspondence to:
Patent Administrator
Testa, Hurwitz & Thibeault, LLP
High Street Tower-125 High Street
Boston, MA 02110
Tel. No.: (617) 248-7000
Fax No.: (617) 248-7100

SIGNATURE BLOCK

Respectfully submitted,

Date: December 15, 2003
Reg. No.: 51,752
Tel. No.: (617) 310-8423
Fax No.: (617) 248-7100

Jennifer Grant Moitoso
Attorney for the Applicants
Testa, Hurwitz & Thibeault, LLP
High Street Tower-125 High Street
Boston, MA 02110

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PATENT
Attorney's Docket No.: EXT-062C1
(2457/62)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Adams *et al.*	**ART UNIT:**	1634
SERIAL NO.:	09/939,275	**EXAMINER:**	Chakrabarti, A.
FILED:	August 24, 2001		
TITLE:	Methods of Purifying DNA Using Immobilized Capture Probes		

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RESPONSE

The following remarks are made in response to the final Office Action dated September 15, 2003 (the "Office Action"). Appropriate fees and forms for a Request for Continued Examination (RCE) are filed herewith. Applicants submit that no extension-of-time, or related fee, is required for this Response to be entered and considered. However, please consider this a conditional petition for the proper extension, if one is required, and a conditional authorization to charge any related extension fees or other fees necessary for entry of this paper to Deposit Account No. 20-0531.

Rejections Under 35 U.S.C. § 103

Claims 1, 5, 7, and 19 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Japanese Unexamined Patent Application No. H3[1991]-47097 (Jiro *et al.*, published February 28, 1991) ("Jiro") in view of Gelfi *et al.*, (November, 1996), Biotechniques, 21:926-932 ("Gelfi") and further in view of Carreira *et al.*, (1980), Analytical Biochemistry, 106: 455-468 ("Carreira"). Claims 2-4, 10-14, and 16 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jiro in view of Gelfi and further in view of Carreira and further in view of U.S. Patent No. 5,482,836 to Cantor *et al.* ("Cantor"). Claims 8, 9, 17, and 18 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jiro in view of Gelfi and further in view of Carreira, and further in view of Cantor and further in view of U.S. Patent No. 4,683,202 to Mullis ("Mullis"). Claims 6 and 15 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jiro in view of Gelfi and further in view of Carreira and further in view of U.S. Patent No.

4,830,726 to Stamato *et al.* ("Stamato"). Claim 20 is rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jiro in view of Gelfi and further in view of Carreira and further in view of U.S. Patent No. 5,478,893 to Ghosh *et al.* ("Ghosh").

Independent claims 1 and 19 recite methods for purifying target molecules from a primer extension sequencing reaction using a purification device. Claims 1 and 19 recite, in part, imposing conditions on the electrophoretic medium that dissociate the targets and their complementary capture probes; applying an electric field while maintaining the dissociating conditions within the electrophoretic medium, thereby causing the dissociated target molecules to exit the electrophoretic medium by electrophoretic migration; and collecting the purified target molecules that have exited the electrophoretic medium (hereinafter "elements c-e"). Independent claim 10 recites a method for purifying multiple sets of primer extension sequencing reaction products which are formed by synthesizing multiple sets of primer extension sequencing reaction products. Elements c-e of claim 10 are similar to elements c-e of independent claims 1 and 19 and will hereafter also be referred to as "elements c-e."

Independent claims 1, 10, and 19 all recite, in part, elements c-e. However, Jiro teaches away from the recited invention and is not properly combinable with any of the other references relied upon in the Office Action (i.e., Gelfi, Carreira, Cantor, Mullis, Stamato, and Ghosh), and each of Jiro, Gelfi, and Carreira, which form the basis of all of the obviousness rejections, lack the motivation to combine with any of the other references relied upon in the Office Action.

Jiro indicates that because the typical hybridization reaction takes place as a result of passive diffusion between a DNA fragment sample fixed on a nitrocellulose membrane (solid phase) and a DNA probe in solution, there has been the problem that the reaction rate is slow and that the operations do not lend themselves to automation (specifically filling and discharge of the several solutions during the reaction and during washing). As a result, it is an object of Jiro to provide a hybridization process and a method for detecting genetic variation employing said method and an apparatus for use therein that are rapid, that lend themselves to automation, wherein hybridization reaction rate is fast, and wherein there are few operations which do not lend themselves to automation, such as filling and discharge of solution and so forth. (Jiro, page 5, paragraphs 1 and 2.) As such, the problem solved, in part, relates to the reaction rate of hybridization and not to elements c-e, including causing dissociated target molecules to exit the

electrophoretic medium and collecting the purified target molecules. In fact, the process of hybridization, by nature, is the opposite of these steps, as hybridization is the binding of two strands of nucleic acid to form a double stranded molecule, and elements c-e involve the dissociation of targets and their complementary capture probes which are collected.

Moreover, Jiro reports on a method in which a nucleic acid probe is fixed on an electrophoretic carrier, nucleic acid samples are made to move within the electrophoretic carrier by electrophoresis, and a hybridization reaction is carried out. After performing the hybridization reaction, portions of the nucleic acid samples that do not bind with perfect complementarity to the fixed probe are removed from the carrier by means of electrophoresis. (Jiro, page 9, paragraph 3.) The portions of the nucleic acid samples that do bind with perfect complementarity remain bound and are subject to a second hybridization reaction with a labeled probe. The labeled probe binds to the nucleic acid sample that is bound to the fixed probe, and the labeled probe is detected. (Jiro, page 9, paragraph 3.)

In contrast to elements c-e, Jiro specifically teaches not to dissociate the perfectly complementary bound nucleic acid from the fixed probe. For example, Jiro teaches heating the electrophoretic carrier to a temperature at which dissociation does not occur if the nucleic acid sample possesses perfect complementarity with respect to the nucleic acid probe. (Jiro, page 6, paragraph 3.) Thus, Jiro actually discourages practice of Applicants' claimed invention because it underscores the critical importance of not dissociating the perfectly complementary bound nucleic acid from the fixed probe to achieve only hybridization, which is antithetical to elements c-e. As such, Jiro is the type of reference which is not properly combinable with any other reference relied upon in the Office Action (i.e., Gelfi, Carreira, Cantor, Mullis, Stamato, and Ghosh). MPEP, § 2145(X)(D)(2).

Furthermore, even if Jiro arguably does not teach away from the claimed invention, for the reasons provided above, Jiro provides no motivation for its combination with the requisite expectation of success with any of the references relied upon in the Office Action insofar as Jiro discourages the artisan from imposing conditions on the electrophoretic medium that dissociate targets and their complementary capture probes. As such, to the extent Jiro was modified to include elements c-e, it would render Jiro unsatisfactory for its intended purpose because the perfectly complementary nucleic acids captured in Jiro would no longer be detectable.

Moreover, the proposed combinations with Jiro to add elements c-e would change the principle of operation of Jiro because Jiro relies upon perfectly complementary nucleic acids remaining bound to fixed probes in order for them to be detected.

Gelfi also provides no motivation for its combination with the requisite expectation of success with any of the references relied upon in the Office Action. In contrast to the recited methods for purifying target molecules from primer extension sequencing reaction products, *i.e.* at least double or single stranded nucleic acid, the sole purpose of Gelfi's method is to detect DNA point mutations by exploiting the differential denaturation temperatures of various DNA duplexes, *i.e.,* wild type–wild type, mutant-mutant, and wild type-mutant. (Gelfi, page 930.) To practice the method of Gelfi, only double stranded DNA molecules are injected into a capillary zone electrophoresis device and a denaturing thermal gradient is generated internally by Joule heat produced by voltage ramps. Point mutations are then fully resolved into a spectrum of four bands. (Gelfi, page 926.) Gelfi actually discourages the methods recited in independent claims 1, 10, and 19 because Gelfi's method is dependent on the characteristics of double stranded DNA from a sample as opposed to primer extension sequencing reaction products that include, at least, double or single stranded nucleic acid. As such, Gelfi lacks any motivation for combination with the other references relied upon in the Office Action because it is limited to examining double stranded DNA.

Carreira also provides no motivation for its combination with the requisite expectation of success with any of the references relied upon in the Office Action. Carreira involves separation and fractionation of a sample of nucleic acid in order to elute fragments of a certain mobility in a particular fraction. In effect, Carreira is separating and collecting certain sizes of nucleic acid fragments in the same step. In contrast, the invention recited in independent claims 1, 10, and 19 involves target molecules binding to immobilized capture probes while non-target molecules continue to migrate, separating target molecules from non-target molecules. At this point in the claimed methods, the target molecules are separated, but not yet collected. In fact, elements c-e are performed in connection with collecting. As such, the principle of operation of Carreira would be altered because Carreira relies on simultaneous separation and collection.

Accordingly, Applicants respectfully submit that Jiro teaches away from the invention recited in independent claims 1, 10, and 19 and that neither Jiro, Gelfi, nor Carreira provide the

motivation with a reasonable expectation of success for combination with any of the references relied upon in the Office action to arrive at the methods recited in independent claims 1, 10, and 19 involving elements c-e, and, as such, independent claims 1, 10, and 19 are allowable. Also, without acquiescing to any of the rejections of the dependent claims, because claims 2-9, 11-18, and 20 depend either directly or indirectly from allowable base claims 1, 10, and/or 19, they also are allowable. In light of the foregoing, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that claims 1-20 are in condition for allowance and request early and favorable action.

Respectfully submitted,

Date: December 15, 2003
Reg. No. 51,752

Jennifer Grant Moitoso
Attorney for the Applicants
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 310-8423
Fax No.: (617) 248-7100